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**Abbreviations:**

BMI: Body mass index

CI: Confidence interval

SD: Standard deviation

SE: Standard error

TLC: Treatment of Lead-exposed Children study

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**Abstract**

Studies in children suggest a weak association between blood lead concentration and blood pressure. To better understand this, we tested the strength of the association in children with elevated blood lead concentrations, and whether succimer chelation changed blood pressure as it did blood lead. In a randomized clinical trial of 780 children with blood lead concentrations of 20-44 μg/dL at age 12-33 months, we compared the systolic and diastolic blood pressure in the succimer-treated group and placebo group for up to 5 years follow-up. We also analyzed the relation of blood lead to blood pressure. Children in the succimer group had lower blood lead concentrations for 9-10 months during and after treatment, but their blood pressure did not differ from those in the placebo group during this period. During 1-5 years follow-up, children in the succimer group had systolic pressures 1.09 (95% confidence interval 0.27, 1.90) mmHg higher than untreated children in a model with repeated measurements, but the difference in diastolic blood pressure was not statistically significant. No association between blood lead and blood pressure was found. Overall, there is no association between blood lead and blood pressure in these children with moderately high lead exposure, nor does chelation with succimer change blood pressure.

Although the causal nature of the relation between lead exposure and elevated blood pressure in adults is still debated (ATSDR 1999; Den Hond et al. 2002; Den Hond et al. 2003; Vupputuri et al. 2003), a meta-analysis of about 60,000 subjects from 31 studies estimated that a doubling of blood lead concentration was associated with a 1.0 (95% confidence interval [CI]: 0.5, 1.4) mmHg rise in systolic pressure and a 0.6 (95% CI: 0.4, 0.8) mmHg rise in diastolic pressure (Nawrot et al. 2002). Children generally have higher blood lead concentrations, but data on the relation between blood lead concentration and blood pressure in them are sparse, and were not included in the meta-analysis because "blood pressure in children is highly variable and correlates highly with height" (Nawrot et al. 2002).

One 1970s study showed that children with blood lead concentrations greater than 40 µg/dL had higher systolic (but not diastolic) blood pressure (Jhaveri et al. 1979), but other studies did not detect any positive association between blood lead and blood pressure in children less than 10 years old (Friedlander et al. 1981; Rogan et al. 1978; Selbst et al. 1993). These early studies all had fewer than 150 subjects and did not adequately control confounding. A contemporary study of 282 children aged 5.5 years in Kosovo, in the former Yugoslavia, did adjust for several covariates with multiple regression (Factor-Litvak et al. 1996). That study showed that a 10 µg/dL increase in blood lead concentration was associated with 0.5 (95% CI: -0.2, 1.3) mmHg increase in systolic and a 0.4 (95% CI: -0.1, 0.9) mmHg increase in diastolic blood pressure (Factor-Litvak et al. 1996). The authors claim that these results suggest but do not demonstrate a weak association (Factor-Litvak et al. 1996).

Blood lead concentration peaks at about age 2 years and then declines, while blood pressure increases with age. It is plausible that the relation between blood lead and blood pressure differs in childhood and adulthood, or that it is unstable in childhood, and thus difficult to characterize with one measurement. Repeated measurements of blood lead and blood pressure in the same child might then be informative. In addition, if lead does increase blood pressure and the effect is acute or subacute and reversible, then the relation will be more apparent when body lead burden changes, such as during chelation.

We used data from a large, randomized study of chelation therapy for lead exposure to answer three questions: 1) Does a sudden and substantial decrease in blood lead induced by chelation have any effect on blood pressure?; 2) Is a sustained but modest lowering of blood lead over a six to nine month period associated with a change in blood pressure?; and 3) Is there any association between concurrent blood lead and blood pressure over five years of follow-up in young children with significant, but variable, lead exposures?

**Materials and methods**

The Treatment of Lead-exposed Children trial is a randomized, placebo-controlled, double-blind clinical trial of 780 children aged 12-33 months (mean age 2 years) with moderately high blood lead concentrations (20-44 μg/dL) to test the effect of chelation on cognitive function and behavior (TLC 1998). Four clinical centers, in Baltimore,

Cincinnati, Newark, and Philadelphia, participated in the enrollment, treatment and follow-up. Three hundred and ninety six children were treated with succimer, an oral lead chelator, for up to three, 26 day rounds (75% of children received a second round of drug, and 81% of those receiving a second round of treatment received a third); 384 were given placebo for similar periods. The study was approved by the institutional review boards at the clinical centers, the Harvard School of Public Health, Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences. The parents of all the children provided written informed consent at enrollment. Succimer decreased blood lead level for several months but had no effect on IQ or neurobehavioral test scores at 36 (about age 5 years) and 60 months (about age 7 years) after initiation of treatment (Dietrich et al. 2004; Rogan et al. 2001).

*Blood lead concentration measurements*

Blood lead concentrations were measured at baseline and days 7, 28, and 42 after the beginning of each round of treatment. Blood lead concentrations were also measured at 3 to 4 month intervals for 5 years of follow-up. The Nutritional Biochemistry Branch at Centers for Disease Control and Prevention in Atlanta did the blood lead analyses by atomic absorption spectrometry based on the methods described by Miller et al (Miller et al. 1987).

*Blood pressure measurements*

At each visit for blood lead measurement, study nurses also measured systolic and diastolic blood pressures. A Dinamap Vital Signs Monitor (an automatic device, Critikon,

Inc., Tampa, FL) was used for all blood pressure measurements. Blood pressure was measured when children were seated. The average of up to three measurements per visit without a notation that the child was crying or not staying still were used for statistical analysis. The overall average number of blood pressure measurements per visit was 2.2. At some visits, i.e., 36 and 60 months follow-up, 3 blood pressure measurements were acquired from all subjects. Study nurses were blinded to treatment status of children.

*Statistical analysis*

We first tested the hypothesis that succimer lowered blood pressure by comparing the succimer and placebo groups immediately after initiation of treatment and in the subsequent follow-ups. Multiple regression models of blood pressure by treatment groups were used to obtain the adjusted difference in blood pressures between treatment and placebo groups at each visit (baseline, during treatment and follow-ups). Covariates adjusted for included clinical center, baseline blood lead concentration, race (black, non-black), sex, parents' education (less than 12 years, 12 years, 13 years and more), single parent (yes, no), age at blood pressure measurement (in years), height and body mass index (BMI) at measurements (Factor-Litvak et al. 1996; Sinaiko 1996). Mixed models with similar covariate adjustment were used to obtain adjusted regression estimates accounting for repeated measurements of blood pressure (using repeated statement in the modeling). The effects of baseline blood lead concentration and age at blood pressure measurement were modeled as fixed effects. Unstructured covariance structure was used in the mixed models by Akaike's Information Criterion. Because the difference in blood lead concentrations between the succimer and placebo groups lasted 9-10 months after

initiation of treatment (see below), the interval from initiation of treatment to 9 months follow-up (not including baseline) and the interval from 12 months to 60 months follow-up were modeled separately.

The trial data set is also a large observational cohort data set, and so we also wanted to examine the relation between blood lead concentration and blood pressure in these data. To do this, we tested whether concurrent blood lead concentration was associated with blood pressure at various time points adjusted for treatment group and other covariates (clinic centers, race, sex, parents' education, single parent, age at blood pressure measurement, height and BMI). Scatter plot of blood pressure by blood lead concentration and plot of residual versus predicted value of regression models supported a linear relation between blood lead concentration and blood pressure, so linear regression models were used. We also did mixed models with repeated blood lead and blood pressure measurements to test their association for two above-mentioned intervals separately.

Software R 2.0 (R 2004) was used for smooth curve fitting and graphics. SAS 9.0 (SAS Inc. Cary, NC) was used for general statistics, multiple regression models and mixed models.

**Results**

Of 780 enrollees, 44% were female, 77% were African-American, 72% lived with single parent, and 40% had parents with less than 12 years of education. At baseline, their mean height was 85.7 (standard deviation [SD]: 5.8) cm, mean BMI was 16.7 (SD: 1.8) kg/m$^2$, and mean age at blood lead and blood pressure measurement was 2.0 (SD: 0.5) years. No difference in these baseline characteristics was seen between treatment groups.

At baseline, the mean blood lead concentration of 780 children was 26 (SD: 5) μg/dL; there was no difference between the succimer and placebo groups in blood lead concentration at baseline. After initiation of treatment, children in the succimer group had lower blood leads than in the placebo group for about 9-10 months. The two groups then had similar blood lead concentrations until the end of study at 60 months follow-up.

Over the 5 years starting from randomization, the children's blood lead concentrations declined by 70% (at 60 months follow-up, the mean blood lead concentration was 8 μg/dL and the standard deviation was 4 μg/dL), but blood pressure changed little. Of 704 children (both succimer and placebo groups combined) that had blood pressure measurement at baseline, the mean systolic blood pressure was 100.7 (SD: 13.5) mmHg and the mean diastolic blood pressure was 60.3 (SD 11.3) mmHg. No difference of blood pressure between succimer and placebo groups at baseline was observed. Figure 1 shows the mean systolic and diastolic blood pressure by treatment group at baseline, day 7, day 42 of the 1$^{st}$ round treatment, 6, 36 and 60 months follow-up. Mean blood lead concentrations (μg/dL) of each group at these time points were inscribed at bottom of each bar. The error bar represents upper bound of the 95% confidence interval of mean

blood pressure. Although the blood lead concentration declined sharply in the succimer group at day 7 of the 1st round treatment, blood pressure in the succimer group did not differ from that in the placebo group. Also, there was no difference in blood pressure between the two treatment groups at other time points. The results of regression models estimating differences in blood pressure between treatment groups (succimer versus placebo) at different time points are shown in table 1. For simplicity, results at only baseline, 1st round treatment, 6, 12, 18, 24, 36 and 60 months follow-up (when more children were measured) are presented. There were slight, statistically significant differences between succimer and placebo groups in systolic blood pressure at the 36 and 60 months follow-up visits, but only after adjustment for covariates. In these multiple regression models, baseline blood lead level was generally not associated with later blood pressure, while height and BMI were usually positively associated with blood pressure. Mixed models with adjustment of covariates showed that, for the interval from initiation of treatment to 9 months follow-up, the overall difference between the succimer and placebo groups is 0.24 (95% CI: -0.79, 1.28) mmHg for systolic blood pressure and 0.46 (95% CI: -0.44, 1.36) mmHg for diastolic blood pressure (both P>0.05). Adjusted mixed models for the interval from 12 months to 60 months follow-up indicated a higher systolic blood pressure for the succimer group; the estimated difference is 1.09 (95% CI: 0.27, 1.90) mmHg (P<0.05); the estimated difference in diastolic blood pressure is 0.15 (95% CI: -0.45, 0.75) mmHg (P>0.05).

The cross-sectional association of blood lead levels and blood pressure were first plotted with data from baseline, 36 months and 60 months follow-up (Figure 2). Spline

regression predictions are also shown in the figure. There was no obvious association between blood lead level and blood pressures at these age points. The parametric regression estimates from baseline, 1st round treatment, 6, 12, 18, 24, 36 and 60 months follow-up are shown in Table 2. At day 7 of the 1st round of treatment, blood lead concentration was associated with systolic blood pressure in an unadjusted analysis, but the association became non-significant after adjustment for covariates. Taking into account repeated measurements of each individual and adjusting for covariates, a mixed model using the interval between initiation of treatment and 9 months follow-up showed regression estimates of -0.16 (95% CI: -0.69, 0.38) mmHg in systolic blood pressure and 0.19 (95% CI: -0.27, 0.66) mmHg in diastolic blood pressure per 10 μg/dL blood lead increase. Using intervals from 12 months to 60 months follow-up, the estimates of per 10 μg/dL blood lead increase were 0.01 (95% CI: -0.57, 0.58) mmHg in systolic blood pressure and 0.003 (95% CI: -0.45, 0.45) mmHg in diastolic blood pressure. None of these estimates in both intervals was statistically significant (all P>0.05)

**Discussion**

Using data from a large clinical trial of children with moderately high lead exposure, we found that succimer treatment did not change blood pressure from initiation of treatment through 9 months after treatment, although it decreased blood lead. In the interval from 1 year after treatment to 5 years after treatment, however, children in the succimer group had a 1 mmHg increase in systolic blood pressure compared with children given placebo; there was no difference in diastolic blood pressure. Analysis of most visits and mixed

models considering repeated measurements did not show any consistent association between concurrent blood lead levels and blood pressures in 2 to 7 year olds. Overall the results suggest no association between blood lead and blood pressure in young children.

Lead exposure in experimental animals induces hypertension (Chai and Webb 1988; Ding et al. 1998; Preuss et al. 1994; Staessen et al. 1994; Victery 1988; Victery et al. 1982b). The possible mechanisms are intracellular perturbation of calcium metabolism at end-arteriole and effects on renin-angiotensin system (Sharp et al. 1987). The lead and blood pressure association has been seen in occupationally exposed workers (de Kort et al. 1987; Telisman et al. 2004), the general adult population (Cheng et al. 2001; Vupputuri et al. 2003), pregnant women (Rothenberg et al. 2002) and peri-menopausal women (Nash et al. 2003), but the literature is not entirely consistent (ATSDR 1999; Hertz-Picciotto and Croft 1993). In children, our study does not support an association between blood lead and blood pressure. The TLC children at enrollment had a mean blood lead concentration of 26 μg/dL, and it could be that the exposure level of lead is not high enough to produce effect on blood pressure. In the Kosovo study, children from the lead-exposed town had blood lead level of 37 μg/dL, while children from the unexposed town had that of 9 μg/dL, but the blood pressure did not differ by town of residence. Also, when data from two towns were combined, the relation between blood lead and blood pressure was not statistically significant (Factor-Litvak et al. 1996). A much higher blood lead concentration (range 40 to 90 μg/dL), as seen in Jhaveri's study of 1-3 year old children, may be detrimental to blood pressure (Jhaveri et al. 1979), but our study could not test this hypothesis. In animal studies, in utero and postnatal exposure

to 100 ppm lead in drinking water increased blood pressure, but exposure to 5 or 25 ppm did not, although renin activity was increased at 25 ppm (Victery et al. 1982a; Victery et al. 1982b). The 100 ppm dose group resulted in a blood lead concentration of 40 µg/dL, while the 25 ppm dose group had an average of 18 µg/dL. The hypertension effect seen in the high dose group may be secondary to the renal lesion caused by continuous high exposure rather than being a direct effect (Victery 1988). Another possible reason for the null association observed in our study is that children with moderate lead exposure may not show elevated blood pressure until a later age, but we do not have data after age 7-8 years. A previous report of 50-year follow-up of children plumbism found a higher risk for hypertension in adulthood compared with controls, suggesting a very long induction period (Hu 1991).

It is also possible that we failed to detect an exisiting relation between blood lead and blood pressure. Although we have largest sample size so far in published studies of blood lead and blood pressure in children (Factor-Litvak et al. 1996; Friedlander et al. 1981; Jhaveri et al. 1979; Rogan et al. 1978; Selbst et al. 1993), we only have power of 0.8 to detect a 2 mmHg difference in blood pressure between treatment and placebo groups for a given cross-sectional comparison. Similarly, for the regression model of blood pressure by blood lead, cross-sectional analysis at each time point was under-powered to detect a shallow slope. We did use repeated measurements of blood lead and blood pressure analyzed with a mixed model in an attempt to mitigate this concern. Even so, in our study, we may not have enough power to detect a slope of 0.5 mmHg per 10 µg/dL blood lead level as seen in Yugoslavia study (Factor-Litvak et al. 1996). Use of an automated blood

pressure monitor in our study is another concern. Although it is not the clinical standard, it can be used as a screening tool or in epidemiologic study of children (Gillman and Cook 1995; NHBPEP 2004). The Yugoslavia study also used automated monitor for blood pressure measurements (Factor-Litvak et al. 1996).

The Treatment of lead-exposed children study was designed to test the hypothesis that children with moderate blood lead levels receiving succimer treatment would have better scores on tests of cognition and behavior than children on placebo. Since no difference in cognitive and behavioral scores was observed between succimer and placebo groups (Dietrich et al. 2004; Rogan et al. 2001), we examined blood pressure, an interesting but not primary outcome in the trial. The finding of no change in blood pressure raises the questions whether the length and dose of treatment were enough to induce changes, whether new exposure to lead was effectively prevented, or whether the lead effects on blood pressure, if they exist, are likely to be reversible. In this trial, we have used higher doses for a longer time than on the Chemet[®] (succimer) label and it is unlikely other chelation regimens are more effective (Rogan et al. 2001). However, even with this dose, only a small portion of total lead body burden was removed because the majority of lead burden is in bone for both children and adults. A longer treatment length (> 3 rounds) may reduce blood lead concentration for a longer time (> 10 months), but the feasibility of such treatment tends to be affected. The houses of TLC children were cleaned up by vacuuming, mopping, minor repairing, and paint stabilization to minimize continuous lead exposure (Rogan et al. 2001). Study in adults indicated that long-term lead accumulation might increase blood pressure and risk of hypertension (Cheng et al. 2001).

We found succimer increased systolic blood pressure from 1 year to 5 years after treatment, but the difference was very small and might have been due to something besides lead, such as calcium excretion from the treatment (Graziano et al. 1988). Calcium intake has been reported to be inversely associated with blood pressure in children (Gillman et al. 1995; Gillman et al. 1992). It may also be that despite of adjustment for covariates, residual confounding (such as genetics, dietary intake) still exists and contributes to the small difference in systolic blood pressure (Sinaiko 1996). Given these uncertainties, a logical step to study the association between lead exposure and blood pressure in children is to seek direct evidence of such an association, preferably by meta-analysis or pooled analysis.

Despite the limitations, this study had larger sample size and repeated measurements, and thus more power and precision than previous studies in children. Common confounders such as age, height, and BMI were adjusted for in the analysis. The proportion of children retained in the TLC study is high, and those who remained in the follow-up did not differ in treatment group, race, sex and socioeconomic status from those lost to follow-up.

The TLC children had much higher blood lead levels than mean of 2 μg/dL in general US children (Pirkle et al. 1998). It is unlikely that background exposure will have effects if the blood lead concentrations in TLC did not. Although there is no clear evidence that the moderate lead exposure experienced by these children affected their blood pressure, the associations between lead exposure and decreased IQ in children and increased blood

pressure in adults render it an important contributor to the global burden of disease

(Fewtrell et al. 2004), hardly diminished by these relatively minor negative findings.

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Table 1 Regression estimates (95% CI) of blood pressure by treatment groups (succimer versus placebo) in TLC children

| Visit | n | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | |
|---|---|---|---|---|---|
| | | Unadjusted | Adjusted[a] | Unadjusted | Adjusted[a] |
| | | $\beta$ (95% CI) | $\beta$ (95% CI) | $\beta$ (95% CI) | $\beta$ (95% CI) |
| Baseline | 704 | -0.54 (-2.54, 1.47) | -0.80 (-2.27, 1.17) | 0.31 (-1.37, 1.98) | 0.15 (-1.50, 1.80) |
| Treatment | | | | | |
| Day 7 of 1st round | 509 | 0.05 (-2.23, 2.33) | -0.37 (-2.58, 1.84) | -0.14 (-2.04, 1.75) | -0.86 (-2.70, 0.99) |
| Day 28 of 1st round | 429 | 0.05 (-2.37, 2.47) | 0.13 (-2.27, 2.53) | 0.77 (-1.33, 2.87) | 0.55 (-1.53, 2.63) |
| Day 42 of 1st round | 631 | 0.81 (-1.04, 2.67) | 0.54 (-1.24, 2.32) | 1.54 (-0.09, 3.16) | 1.16 (-0.43, 2.76) |
| Follow-up | | | | | |
| 6 months | 365 | 1.19 (-1.04, 3.43) | 1.10 (-1.02, 3.21) | 1.44 (-0.37, 3.24) | 1.32 (-0.48, 3.11) |
| 12 months | 597 | 0.87 (-0.77, 2.51) | 0.87 (-0.66, 2.40) | 0.90 (-0.31, 2.12) | 0.87 (-0.36, 2.09) |
| 18 months | 335 | 0.76 (-1.23, 2.75) | 0.89 (-0.95, 2.73) | -0.48 (-1.94, 0.98) | -0.44 (-1.88, 1.01) |
| 24 months | 607 | 0.40 (-1.10, 1.90) | 0.64 (-0.66, 1.94) | -0.81 (-1.88, 0.25) | -0.79 (-1.81, 0.23) |
| 36 months | 647 | 0.43 (-1.08, 1.95) | 1.27 (0.06, 2.48)[*] | 0.54 (-0.49, 1.57) | 0.74 (-0.26, 1.74) |
| 60 months | 569 | 1.57 (-0.09, 3.22) | 1.69 (0.34, 3.04)[*] | 0.36 (-0.78, 1.50) | 0.30 (-0.80, 1.39) |

[a] Adjusted for clinical center, baseline blood lead level, race, sex, parents' education, single parent, age at test, height and body mass index

[*] $P<0.05$

Table 2 Regression estimates (95% CI) of blood pressure change per 10 μg/dL of elevation in concurrent blood lead level in TLC children

| Visit | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | |
| --- | --- | --- | --- | --- |
| | Unadjusted $\beta$ (95% CI) | Adjusted[a] $\beta$ (95% CI) | Unadjusted $\beta$ (95% CI) | Adjusted[a] $\beta$ (95% CI) |
| Baseline | 1.19 (-0.76, 3.15) | 1.36 (-0.58, 3.30) | 1.25 (-0.38, 2.88) | 1.47 (-0.16, 3.10) |
| Treatment | | | | |
| Day 7 of 1st round | 1.41 (0.13, 2.69)* | 1.26 (-0.27, 2.78) | 1.05 (-0.01, 2.12) | 1.14 (-0.13, 2.41) |
| Day 28 of 1st round | 0.02 (-1.50, 1.53) | 0.21 (-1.53, 1.95) | 0.22 (-1.10, 1.54) | 0.73 (-0.78, 2.23) |
| Day 42 of 1st round | -0.27 (-1.69, 1.15) | 0.07 (-1.33, 1.47) | 0.69 (-0.56, 1.94) | 1.19 (-0.07, 2.44) |
| Follow-up | | | | |
| 6 months | 1.14 (-0.68, 2.95) | 0.62 (-1.13, 2.37) | 0.41 (-1.06, 1.88) | 0.33 (-1.15, 1.81) |
| 12 months | 0.48 (-0.81, 1.77) | 0.24 (-0.97, 1.46) | -0.29 (-1.24, 0.66) | -0.28 (-1.26, 0.69) |
| 18 months | 0.73 (-0.90, 2.36) | 0.81 (-0.70, 2.31) | -0.30 (-1.50, 0.89) | -0.34 (-1.52, 0.85) |
| 24 months | -0.27 (-1.47, 0.94) | -0.68 (-1.76, 0.39) | 0.14 (-0.71, 1.00) | 0.32 (-0.52, 1.16) |
| 36 months | 0.08 (-1.38, 1.54) | -0.72 (-1.91, 0.48) | -0.37 (-1.36, 0.63) | -0.44 (-1.43, 0.56) |
| 60 months | -0.17 (-2.19, 1.85) | 0.01 (-1.71, 1.73) | -0.34 (-1.72, 1.05) | 0.15 (-1.25, 1.55) |

[a] Adjusted for clinical center, treatment group, race, sex, parents' education, single parent, age at test, height and body mass index

* $P<0.05$

Figure legends


Figure 1. Systolic and Diastolic blood pressure by treatment group at baseline, day 7 and

42 of 1<sup>st</sup> round treatment, 6, 36 and 60 months follow-up in TLC children

Error bar represents upper bound of 95% confidence interval of the mean blood pressure

Blood lead concentrations (μg/dL) of each group at these time points were inscribed at

bottom of the bar chart.


Figure 2. Systolic and diastolic blood pressure by concurrent blood lead concentration at

baseline, 36 and 60 months follow-up

Green circles are scatter plot of systolic blood pressure; blue circles are scatter plot of

diastolic blood pressure. Black lines are spline regression estimates without covariates

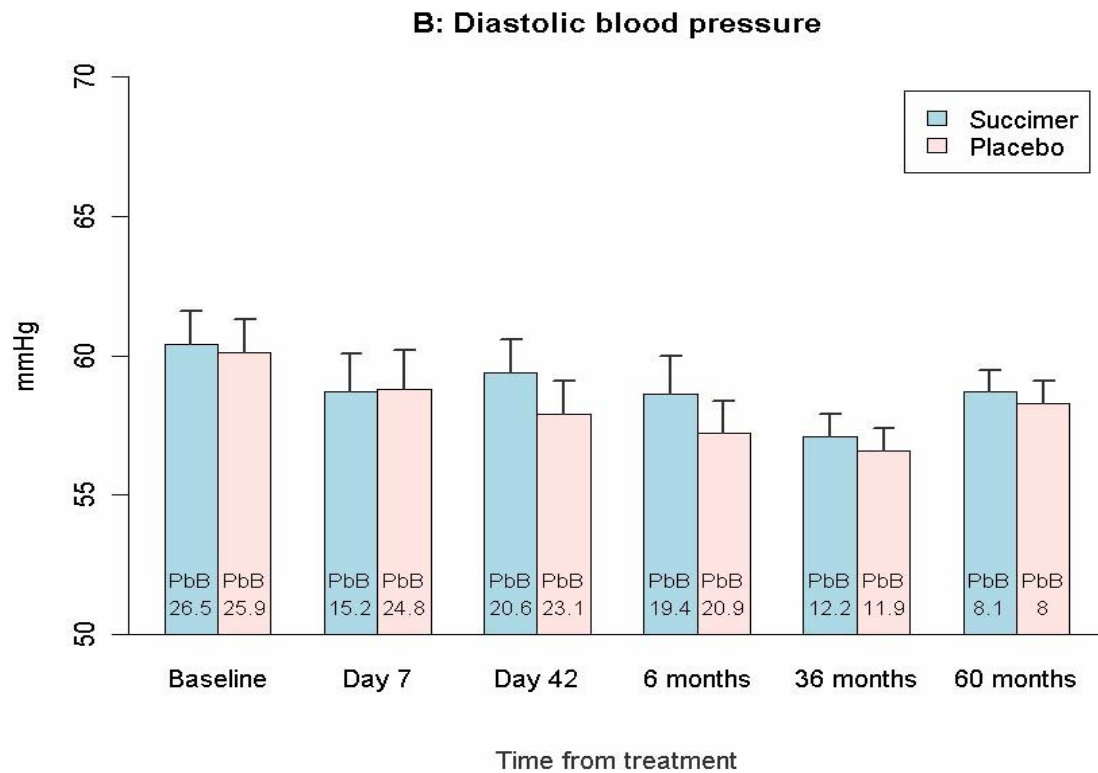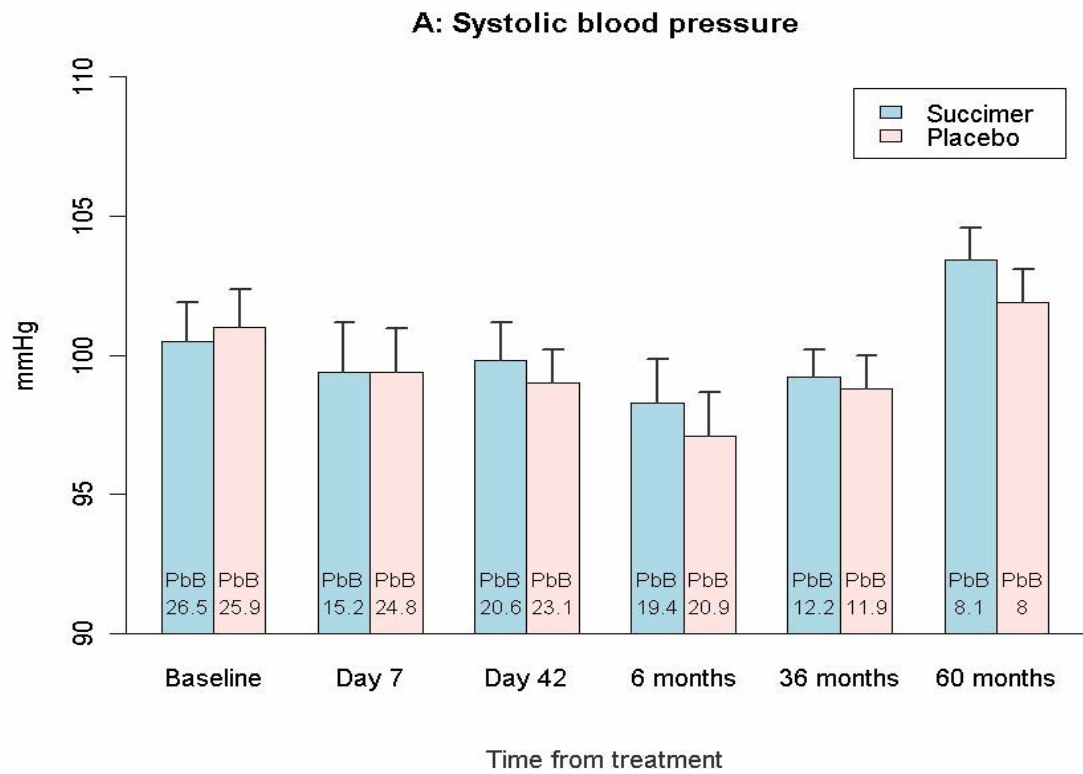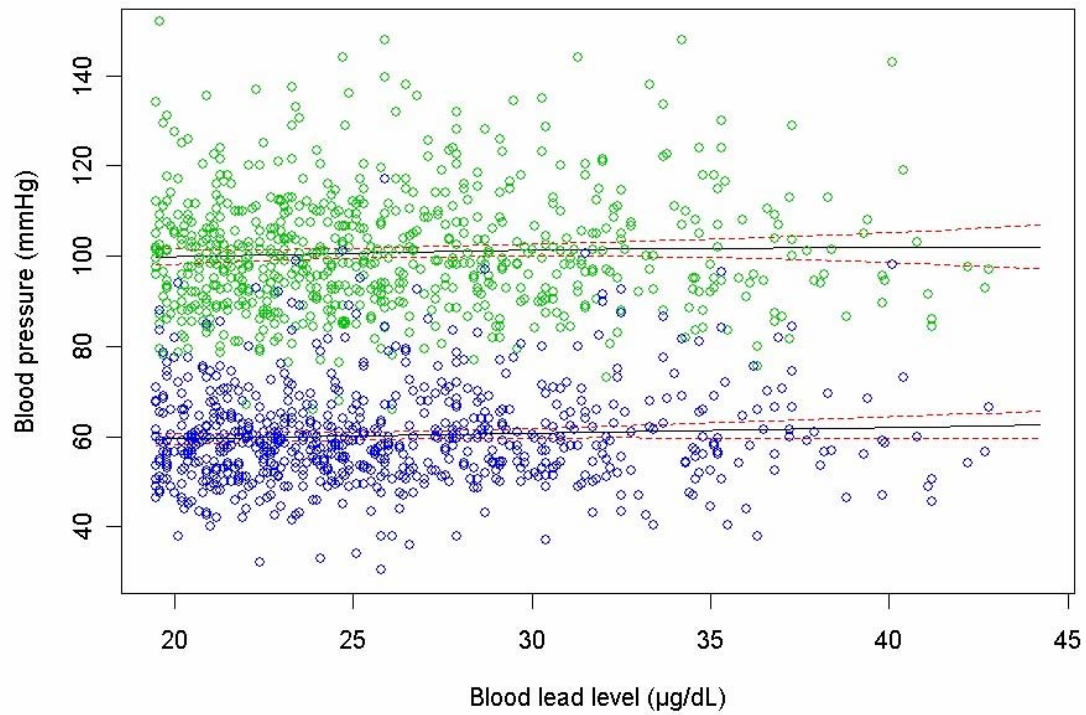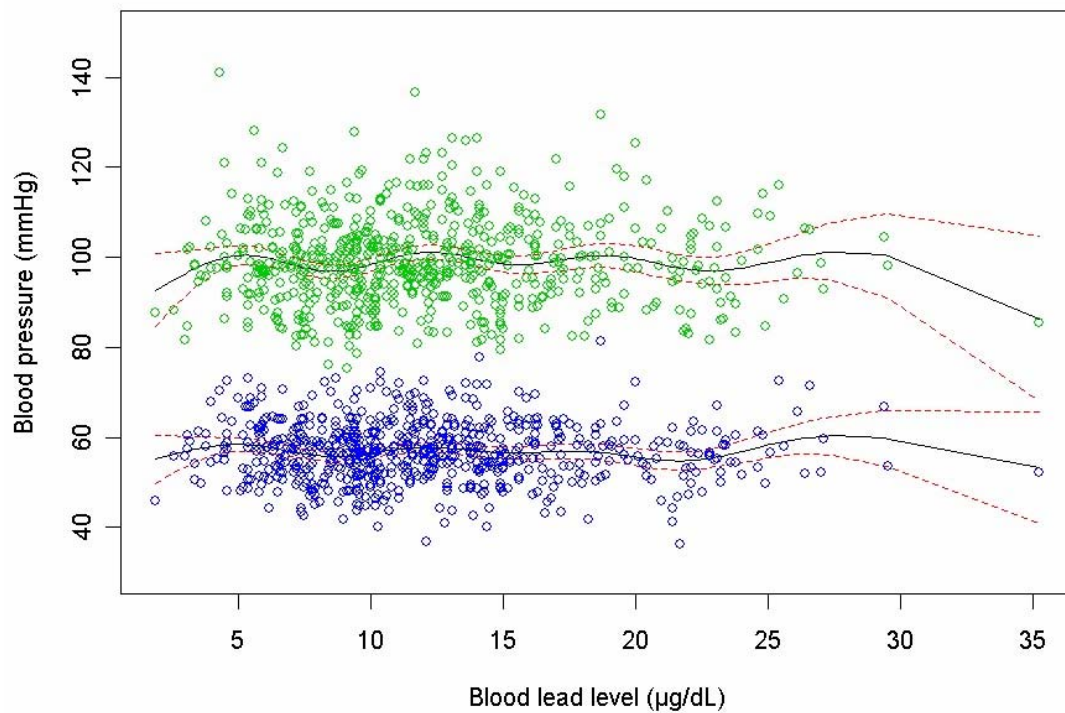adjustment and red dotted lines are their 95% confidence intervals.

**A: Systolic blood pressure**

**B: Diastolic blood pressure**

Figure 1

**A: Systolic and diastolic blood pressure by blood lead at baseline**

**B: Systolic and diastolic blood pressure by blood lead at 36 months follow-up**

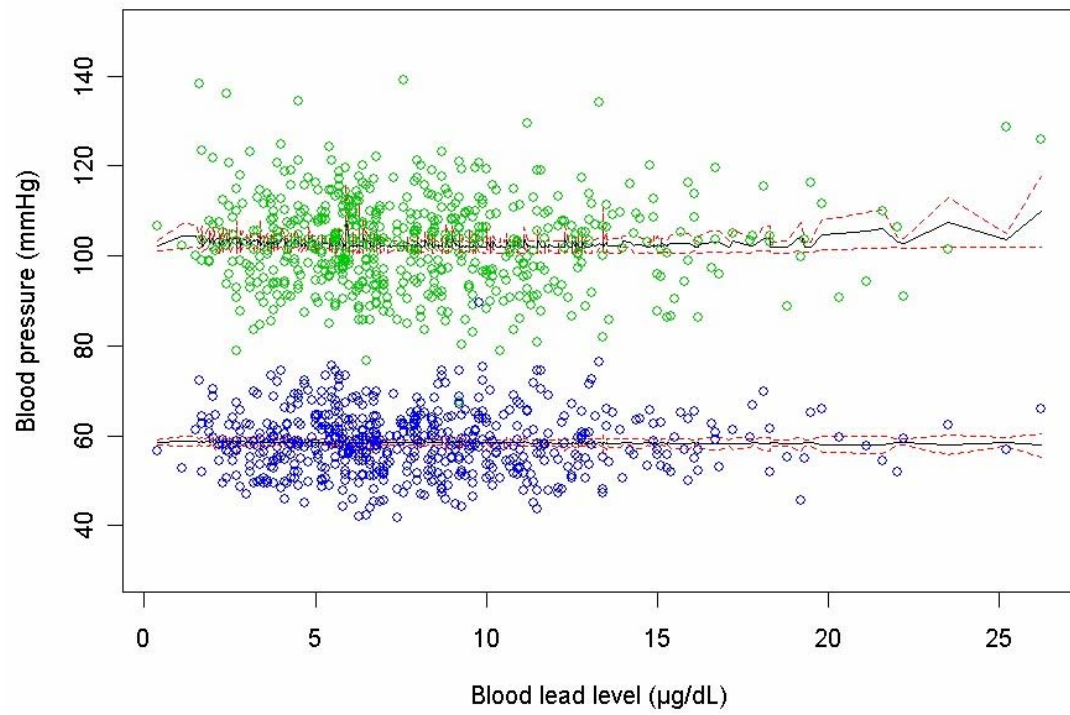## C: Systolic and diastolic blood pressure by blood lead at 60 months follow-up



Figure 2